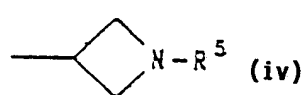
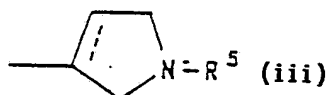
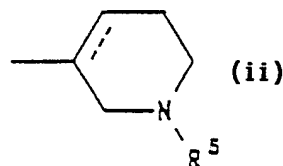
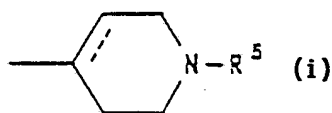
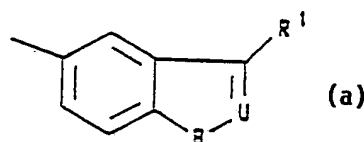
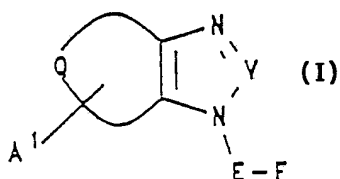




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(54) Title: FUSED IMIDAZOLE AND TRIAZOLE DERIVATIVES AS 5-HT₁ RECEPTOR AGONISTS**(57) Abstract**

Compounds of formula (I) wherein Q represents the residue of a six-membered aromatic or heteroaromatic nucleus containing zero, one or two nitrogen atoms; V represents nitrogen or C-A²; E represents a bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms; F represents a group of formula (a); U represents nitrogen or C-R²; B represents oxygen, sulphur or N-R³; R¹ represents -CH₂.CHR⁴.NR⁶R⁷ or a group of formula (i), (ii), (iii) or (iv); are selective agonists of 5-HT₁-like receptors and are therefore useful in the treatment of clinical conditions, in particular migraine and associated disorders, for which a selective agonist of these receptors is indicated.

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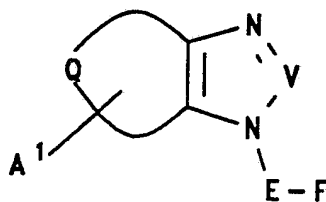
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FUSED IMIDAZOLE AND TRIAZOLE DERIVATIVES AS 5-HT₁ RECEPTOR AGONISTS

The present invention relates to a class of fused imidazole and triazole derivatives which act on 5-hydroxytryptamine (5-HT) receptors, being selective agonists of so-called "5-HT₁-like" receptors. They are therefore useful in the treatment of clinical conditions for which a selective agonist of these receptors is indicated.

5-HT₁-like receptor agonists which exhibit selective vasoconstrictor activity have recently been described as being of use in the treatment of migraine (see, for example, A. Doenicke *et al.*, The Lancet, 1988, Vol. 1, 1309-11). The compounds of the present invention, being selective 5-HT₁-like receptor agonists, are accordingly of particular use in the treatment of migraine and associated conditions, e.g. cluster headache, chronic paroxysmal hemicrania, headache associated with vascular disorders, tension headache and paediatric migraine.

The present invention provides a compound of formula I, or a salt or prodrug thereof:



(I)

wherein

Q represents the residue of a six-membered aromatic or heteroaromatic nucleus containing zero, one or two nitrogen atoms;

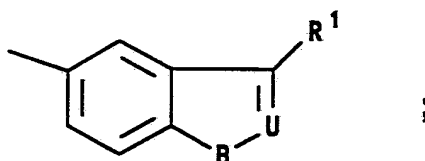
- 2 -

A¹ represents hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, -OR^x, -SR^x, -NR^xR^y, -NR^xCOR^y, -NR^xCO₂R^y, -NR^xSO₂R^y, or -NR^zCTNR^xR^y;

5 V represents nitrogen or C-A²;

E represents a bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms;

F represents a group of formula



U represents nitrogen or C-R²;

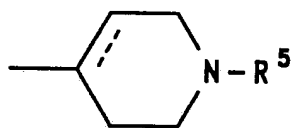
B represents oxygen, sulphur or N-R³;

20 R¹ represents -CH₂.CHR⁴.NR⁶R⁷ or a group of formula (i), (ii), (iii) or (iv):

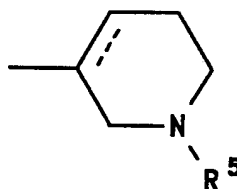
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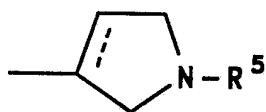
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(I)



(II)



(III)



(IV)

in which the broken line represents an optional chemical bond;

20 A^2 , R^2 , R^3 , R^4 , R^5 , R^6 and R^7 independently represent hydrogen or C_{1-6} alkyl;

R^x and R^y independently represent hydrogen, hydrocarbon or a heterocyclic group, or R^x and R^y together represent a C_{2-6} alkylene group;

25 R^z represents hydrogen, hydrocarbon or a heterocyclic group;

T represents oxygen, sulphur or a group of formula $=N.G$; and

G represents hydrocarbon, a heterocyclic group or an electron-withdrawing group.

30 For use in medicine, the salts of the compounds of formula I will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their non-toxic pharmaceutically

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acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, sulphuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid.

Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The term "hydrocarbon" as used herein includes straight-chained, branched and cyclic groups containing up to 18 carbon atoms, suitably up to 15 carbon atoms, and conveniently up to 12 carbon atoms. Suitable hydrocarbon groups include C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, aryl and aryl(C₁₋₆)alkyl.

The expression "a heterocyclic group" as used herein includes cyclic groups containing up to 18 carbon atoms and at least one heteroatom preferably selected from oxygen, nitrogen and sulphur. The heterocyclic group suitably contains up to 15 carbon atoms and conveniently up to 12 carbon atoms, and is preferably linked through carbon. Examples of suitable heterocyclic groups include C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, heteroaryl and heteroaryl(C₁₋₆)alkyl groups.

Suitable alkyl groups include straight-

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chained and branched alkyl groups containing from 1 to 6 carbon atoms. Typical examples include methyl and ethyl groups, and straight-chained or branched propyl and butyl groups. Particular alkyl groups are methyl, ethyl and t-butyl.

Suitable alkenyl groups include straight-chained and branched alkenyl groups containing from 2 to 6 carbon atoms. Typical examples include vinyl and allyl groups.

Suitable alkynyl groups include straight-chained and branched alkynyl groups containing from 2 to 6 carbon atoms. Typical examples include ethynyl and propargyl groups.

Suitable cycloalkyl groups include groups containing from 3 to 7 carbon atoms. Particular cycloalkyl groups are cyclopropyl and cyclohexyl.

A particular aryl group is phenyl.

Particular aryl(C₁₋₆)alkyl groups include benzyl, phenethyl and phenylpropyl.

Suitable heterocycloalkyl groups include azetidiny, pyrrolidyl, piperidyl, piperazinyl and morpholinyl groups.

Suitable heteroaryl groups include pyridyl, quinolyl, isoquinolyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, imidazolyl, oxadiazolyl and thiadiazolyl groups.

Particular heteroaryl(C₁₋₆)alkyl groups include pyridylmethyl and pyrazinylmethyl.

The hydrocarbon and heterocyclic groups may in turn be optionally substituted by one or more groups selected from C₁₋₆ alkyl, adamantyl, phenyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ aminoalkyl, trifluoromethyl, hydroxy, C₁₋₆ alkoxy, aryloxy, keto, C₁₋₃ alkylenedioxy, nitro, cyano,

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carboxy, C₂₋₆ alkoxy carbonyl, C₂₋₆ alkoxy carbonyl(C₁₋₆)alkyl, C₂₋₆ alkyl carbonyloxy, aryl carbonyloxy, C₂₋₆ alkyl carbonyl, aryl carbonyl, C₁₋₆ alkylthio, C₁₋₆ alkylsulphinyl, C₁₋₆ alkylsulphonyl, arylsulphonyl, NR^VR^W, -NR^VCOR^W, -NR^VCO₂R^W,
5 -NR^VSO₂R^W, -CH₂NR^VSO₂R^W, -NHCONR^VR^W, -CONR^VR^W, -SO₂NR^VR^W and -CH₂SO₂NR^VR^W, in which R^V and R^W independently represent hydrogen, C₁₋₆ alkyl, aryl or aryl(C₁₋₆)alkyl, or R^V and R^W together represent a C₂₋₆ alkylene group.

When R^X and R^Y, or R^V and R^W, together represent
10 a C₂₋₆ alkylene group, this group may be an ethylene, propylene, butylene, pentamethylene or hexamethylene group, preferably butylene or pentamethylene.

When the group G represents an electron-withdrawing group, this group is suitably cyano, nitro,
15 -COR^X, -CO₂R^X or -SO₂R^X, in which R^X is as defined above.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially fluorine.

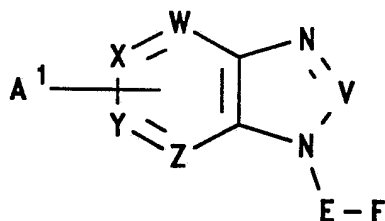
The present invention includes within its scope
20 prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily convertible in vivo into the required compound of formula I. Conventional procedures for the selection and preparation
25 of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

Where the compounds according to the invention have at least one asymmetric centre, they may accordingly
30 exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures

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thereof are encompassed within the scope of the present invention.

The six-membered aromatic or heteroaromatic nucleus of which Q is the residue in the compounds of formula I as defined above is a benzene, pyridine,
 5 pyridazine, pyrimidine or pyrazine nucleus. Thus, the compounds of formula I may suitably be represented by structure IA:



(IA)

in which zero, one or two of W, X, Y and Z represent nitrogen and the remainder represent carbon; and A¹, V, E and F are as defined above.

20 In a suitable embodiment, W represents nitrogen, X and Z each represents carbon and Y represents nitrogen or carbon.

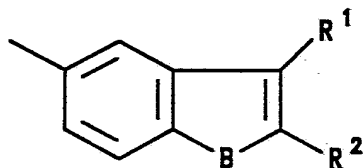
In an alternative embodiment, Z represents nitrogen, W and Y each represents carbon and X represents
 25 nitrogen or carbon.

Preferably, V represents CH.

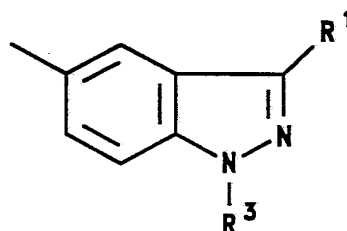
The alkylene chain E may be, for example, methylene, ethylene, 1-methylethylene, propylene or 2-methylpropylene. Alternatively, the group E may
 30 represent a single bond such that the group F in formula I is attached directly to the five-membered heteroaromatic ring.

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The group F is suitably an indole, benzofuran or benzthiophene moiety of formula FA, or an indazole moiety of formula FB:



(FA)

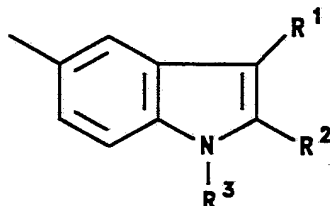


(FB)

wherein B, R¹, R² and R³ are as defined above.

Preferably, the group F represents an indole moiety of structure FC:

15



(FC)

wherein R¹, R² and R³ are as defined above, in particular wherein R² and R³ are both hydrogen.

25

Suitable values for the group A¹ include C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, heteroaryl, heteroaryl(C₁₋₆)alkyl, C₁₋₆ alkoxy or C₁₋₆ alkylthio, any of which groups may be optionally substituted; and hydrogen, halogen, cyano, trifluoromethyl or -NR^xR^y, in which R^x and R^y are as defined above. Examples of optional substituents on the group A¹ suitably include trifluoromethyl, C₁₋₆ alkoxy, C₂₋₆ alkoxy carbonyl, C₂₋₆ alkyl carbonyl, C₁₋₆ alkylsulphonyl, arylsulphonyl, amino, mono- or di(C₁₋₆)alkylamino, C₂₋₆

30

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alkylcarbonylamino, arylcarbonylamino, C₂₋₆
alkoxycarbonylamino, C₁₋₆ alkylsulphonylamino,
arylsulphonylamino, C₁₋₆ alkylsulphonylaminomethyl,
aminocarbonylamino, mono- or
5 di(C₁₋₆)alkylaminocarbonylamino, mono- or
diarylaminocarbonylamino, pyrrolidylcarbonylamino,
aminocarbonyl, mono- or di(C₁₋₆)alkylaminocarbonyl, C₁₋₆
alkylaminosulphonyl, aminosulphonylmethyl, and mono- or
di(C₁₋₆)alkylaminosulphonylmethyl.

10 Particular values of A¹ include hydrogen,
methyl, methoxymethyl, aminomethyl, dimethylaminomethyl,
acetylaminomethyl, benzoylaminomethyl, t-
butoxycarbonylaminomethyl, methylsulphonylaminomethyl,
phenylsulphonylaminomethyl, aminocarbonylmethyl, ethyl,
15 aminoethyl, acetylaminomethyl, benzoylaminomethyl,
methoxycarbonylaminomethyl, ethoxycarbonylaminomethyl,
t-butoxycarbonylaminomethyl, methylsulphonylaminomethyl,
aminocarbonylaminomethyl, methylaminocarbonylaminomethyl,
t-butylaminocarbonylaminomethyl, phenylaminocarbonyl-
20 aminoethyl, pyrrolidylcarbonylaminomethyl, cyclopropyl,
phenyl, methylsulphonylaminophenyl, aminocarbonylphenyl,
methylaminocarbonylphenyl, methylsulphonylaminomethyl-
phenyl, aminosulphonylmethylphenyl, methylaminosulphonyl-
methylphenyl, dimethylaminosulphonylmethylphenyl, benzyl,
25 trifluoromethylbenzyl, methoxybenzyl, acetylaminobenzyl,
methylsulphonylaminobenzyl, aminocarbonylaminobenzyl,
aminocarbonylbenzyl, methylaminocarbonylbenzyl,
methylsulphonylbenzyl, methylaminosulphonylbenzyl,
pyridylmethyl, methoxypyridylmethyl, amino, methylamino,
30 benzylamino, dimethylamino, t-butoxycarbonylamino-
ethylamino and methylsulphonylaminoethylamino.

Preferably, A¹ is hydrogen.

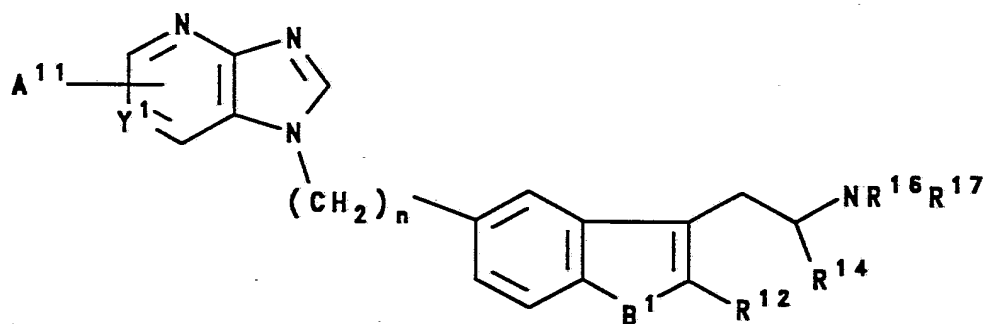
Representative values of R¹ include aminoethyl,
N-methylaminoethyl, N,N-dimethylaminoethyl, 4-piperidyl,

- 10 -

1-methyl-4-piperidyl, 3-pyrrolidinyl, 1-methyl-3-pyrrolidinyl, 3-azetidyl and 1-methyl-3-azetidyl.

Preferred values for the groups R^2 to R^7 are hydrogen and methyl.

5 A particular sub-class of compounds according to the invention is represented by the compounds of formula IIA, and salts and prodrugs thereof:



(IIA)

wherein

- 20 Y^1 represents nitrogen or carbon;
 n is zero, 1, 2 or 3;
 B^1 represents oxygen, sulphur or $N-R^{13}$;
 A^{11} represents C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7}
25 heterocycloalkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylamino or di(C_{1-6})alkylamino, any of which groups may be optionally substituted; or hydrogen, halogen, cyano, trifluoromethyl or amino; and
30 R^{12} , R^{13} , R^{14} , R^{16} and R^{17} independently represent hydrogen or C_{1-6} alkyl.

Examples of optional substituents on the group A^{11} suitably include trifluoromethyl, C_{1-6} alkoxy, C_{2-6} alkoxy carbonyl, C_{2-6} alkyl carbonyl, C_{1-6} alkylsulphonyl,

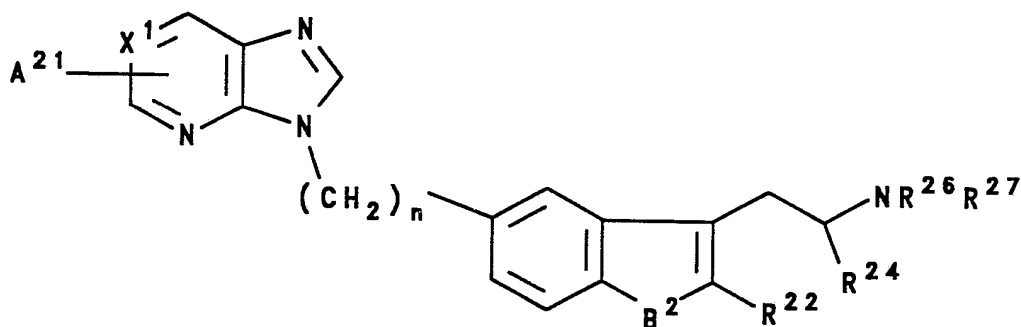
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arylsulphonyl, amino, mono- or di(C₁₋₆)alkylamino, C₂₋₆
 alkylcarbonylamino, arylcarbonylamino, C₂₋₆
 alkoxycarbonylamino, C₁₋₆ alkylsulphonylamino,
 arylsulphonylamino, C₁₋₆ alkylsulphonylaminomethyl,
 5 aminocarbonylamino, mono- or di(C₁₋₆)alkylamino-
 carbonylamino, mono- or diarylamino carbonylamino,
 pyrrolidylcarbonylamino, aminocarbonyl, mono- or
 di(C₁₋₆)alkylaminocarbonyl, C₁₋₆ alkylaminosulphonyl,
 aminosulphonylmethyl, and mono- or di(C₁₋₆)alkyl-
 10 aminosulphonylmethyl.

Preferably, A¹¹ is hydrogen.

Preferably, R¹², R¹³ and R¹⁴ each represents
 hydrogen. Preferred values of R¹⁶ and R¹⁷ with respect to
 formula IIA include hydrogen and methyl.

15 Another sub-class of compounds according to the
 invention is represented by the compounds of formula IIB,
 and salts and prodrugs thereof:



(I I B)

wherein

30

- X¹ represents nitrogen or carbon;
- n is zero, 1, 2 or 3;
- B² represents oxygen, sulphur or N-R²³;
- A²¹ represents C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆
 alkynyl, C₃₋₇ cycloalkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇

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heterocycloalkyl, heteroaryl, heteroaryl(C₁₋₆)alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkylamino or di(C₁₋₆)alkylamino, any of which groups may be optionally substituted; or hydrogen, halogen, cyano, trifluoromethyl or amino; and

R²², R²³, R²⁴, R²⁶ and R²⁷ independently represent hydrogen or C₁₋₆ alkyl.

Examples of optional substituents on the group A²¹ correspond to those indicated for the group A¹¹ with respect to formula IIA above. Preferably, A²¹ is hydrogen.

Preferably, R²², R²³ and R²⁴ each represents hydrogen. Preferred values of R²⁶ and R²⁷ with respect to formula IIB include hydrogen and methyl.

Specific compounds within the scope of the present invention include:

N,N-dimethyl-2-[5-(4-azabenzimidazol-1-yl)-1H-indol-3-yl]ethylamine;

N,N-dimethyl-2-[5-(4,6-diazabenzimidazol-1-yl)-1H-indol-3-yl]ethylamine;

N,N-dimethyl-2-[5-(4,6-diazabenzimidazol-1-ylmethyl)-1H-indol-3-yl]ethylamine;

N,N-dimethyl-2-[5-(5,7-diazabenzimidazol-1-ylmethyl)-1H-indol-3-yl]ethylamine;

and salts and prodrugs thereof.

The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal

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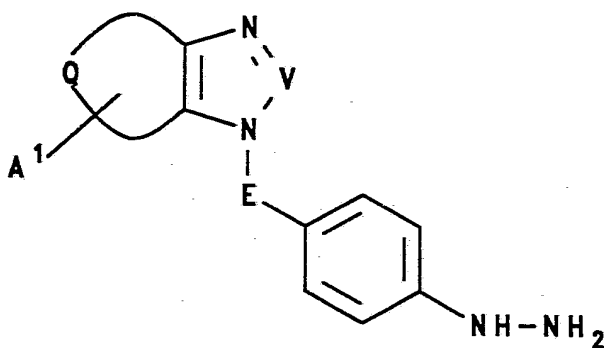
administration, or for administration by inhalation or insufflation. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

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The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone or gelatin.

In the treatment of migraine, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

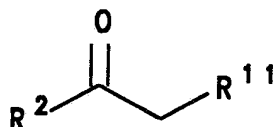
The compounds according to this invention wherein the group F is an indole moiety of structure FC as defined above may be prepared by a process which comprises reacting a compound of formula III:



(III)

- 15 -

wherein Q, A¹, V and E are as defined above; with a compound of formula IV or a carbonyl-protected form thereof:



(IV)

10 wherein R² is as defined above and R¹¹ corresponds to the group R¹ as defined above or a protected derivative thereof, or represents a group of formula -CH₂.CHR⁴D¹, in which R⁴ is as defined above and D¹ represents a readily
15 displaceable group; followed, where required, by N-alkylation by standard methods to introduce the moiety R³; and, if necessary, by removal of any protecting groups.

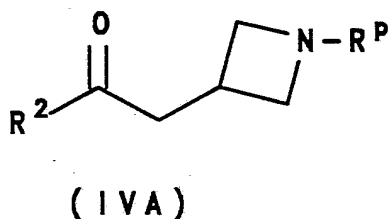
Suitable carbonyl-protected forms of the compounds of formula IV include the dimethyl acetal or
20 ketal derivatives.

The readily displaceable group D¹ in the compounds of formula IV suitably represents a halogen atom, preferably chlorine. When the moiety R¹¹ in the compounds of formula IV is a group of formula -CH₂.CHR⁴D¹,
25 the substituent D¹ is displaced in situ under the prevailing reaction conditions to afford a final product of formula I wherein R¹ represents a group of formula -CH₂.CHR⁴.NH₂. The terminal amino group can subsequently, if desired, be further elaborated using techniques known
30 from the art to give a compound of formula I wherein R¹ represents the required group of formula -CH₂.CHR⁴.NR⁶R⁷.

Where R¹ in the final product of formula I represents an azetidiny moiety of formula (iv) as hereinbefore defined, the reagent of formula IV of use in

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the above reaction, in which R^{11} corresponds to a protected derivative of the group R^1 , may suitably be represented by structure IVA:



10 wherein R^2 is as defined above and R^P represents an amino-protecting group.

Suitable examples of amino-protecting groups for the substituent R^P include carboxylic acid groups such as chloroacetyl, trifluoroacetyl, formyl, benzoyl, phthaloyl, phenylacetyl or pyridinecarbonyl; acid groups
 15 derived from carbonic acid such as ethoxycarbonyl, benzyloxycarbonyl, t-butoxycarbonyl, biphenylisopropoxycarbonyl, p-methylbenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, p-phenylazobenzyloxycarbonyl, p-(p'-methoxyphenylazo)benzyloxycarbonyl or t-amyloxycarbonyl; acid groups derived from sulphonic acid,
 20 e.g. p-toluenesulphonic acid; and other groups such as benzyl, p-methoxybenzyl, trityl, o-nitrophenylsulphenyl or benzylidene.

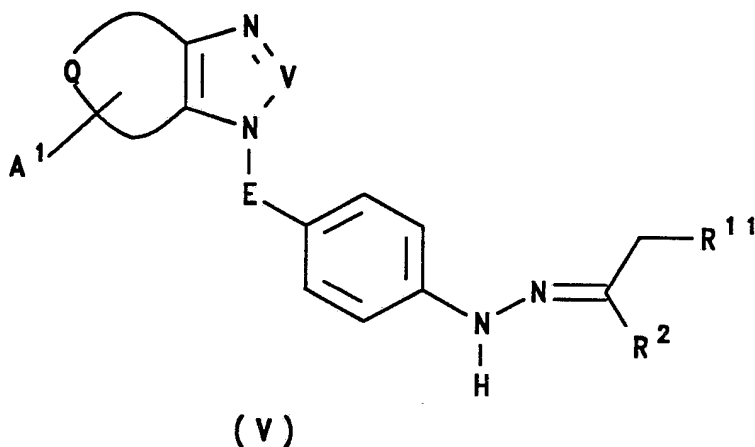
25 Preferred amino-protecting groups include t-butoxycarbonyl, benzyloxycarbonyl and p-methoxybenzyl.

The removal of the protecting group present in the resultant compound may be effected by an appropriate procedure depending upon the nature of the protecting
 30 group. Typical procedures include hydrogenation in the presence of a palladium catalyst (e.g. palladium carbon or palladium black) for benzyloxycarbonyl, p-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, p-phenylazobenzyloxycarbonyl, p-(p'-methoxyphenylazo)benzyloxy-

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carbonyl and trityl groups; treatment with hydrogen
bromide in glacial acetic acid or trifluoroacetic acid
for benzyloxycarbonyl, p-bromobenzyloxycarbonyl, p-
phenylazobenzyloxycarbonyl and t-butoxycarbonyl groups;
5 treatment with acetic acid and/or a mineral acid such as
hydrochloric acid or sulphuric acid for trityl, t-
butoxycarbonyl, formyl and benzylidene groups; and
treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
for p-methoxybenzyl groups.

10 The reaction of compounds III and IV may be
carried out in a single step (Fischer indole synthesis)
or by an initial non-cyclising step at a lower
temperature to give a compound of formula V:

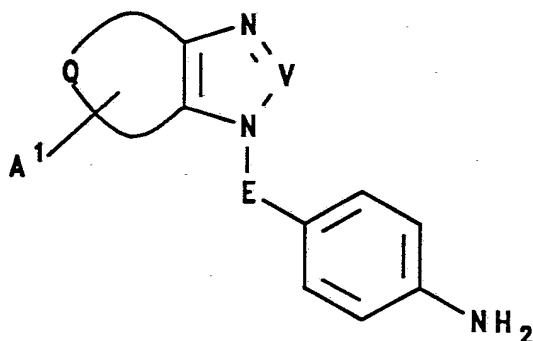


25 wherein Q, A¹, V, E, R² and R¹¹ are as defined above;
followed by cyclisation using a suitable reagent, such as
a polyphosphate ester.

The hydrazines of formula III may be prepared
from the corresponding anilines of formula VI:

30

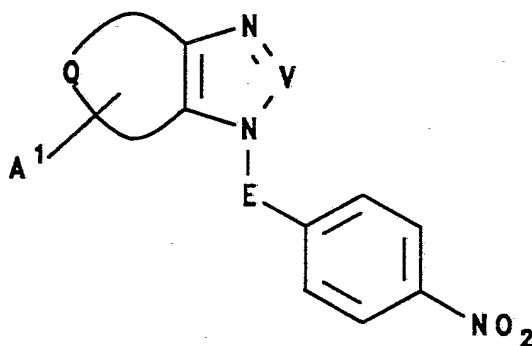
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(VI)

wherein Q, A¹, V and E are as defined above; by
diazotisation followed by reduction. Diazotisation is
typically carried out using sodium nitrite/conc. HCl and
the resulting diazo product reduced in situ using, for
example, tin(II) chloride/conc. HCl, sodium
sulphite/conc. HCl, or sodium sulphite/conc. H₂SO₄.

The anilines of formula VI may be prepared by
reduction of the corresponding nitro compounds of formula
VII:



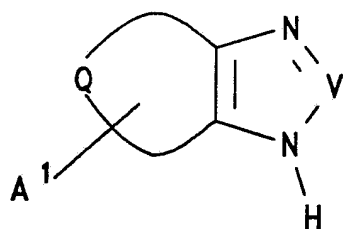
(VII)

wherein Q, A¹, V and E are as defined above; typically by
transfer hydrogenation using a hydrogenation catalyst
such as palladium on charcoal in the presence of a

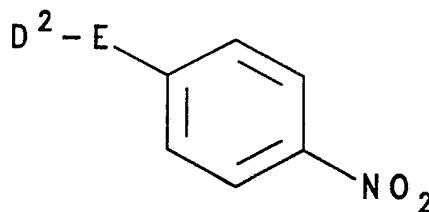
- 19 -

hydrogen donor such as ammonium formate, or alternatively by conventional catalytic hydrogenation or using tin(II) chloride.

5 The nitro compounds of formula VII may be prepared by a variety of methods which will be readily apparent to those skilled in the art. One such method involves reacting a compound of formula VIII with a compound of formula IX:



(VIII)



(IX)

wherein Q, A¹, V and E are as defined above, and D² represents a readily displaceable group.

20 The reaction is conveniently carried out in the presence of sodium hydride using N,N-dimethylformamide as solvent.

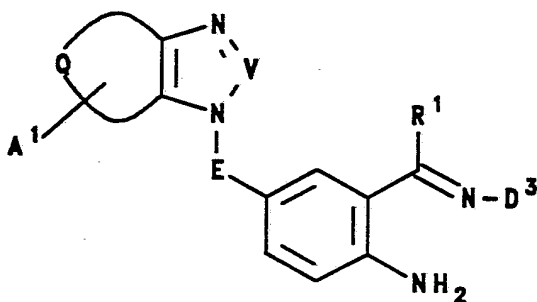
25 The readily displaceable group D² in the compounds of formula IX is suitably a halogen atom, preferably bromine; except when the moiety D² is attached directly to the aromatic ring, i.e. when E represents a bond, in which case D² is preferably fluorine.

30 It will be appreciated that a mixture of positional isomers is obtainable from the reaction between compounds VIII and IX, since nucleophilic displacement of the group D² by either of the two nitrogen atoms depicted in the five-membered ring in formula VIII is roughly equally likely in principle. This will be so unless the six-membered ring of which Q

- 20 -

is the residue is symmetrical, i.e. unless the pairs of atoms W/Z and X/Y as depicted in structure IA above are identical and A¹ is hydrogen. Where a mixture of isomers is indeed obtained from this reaction, separation of the isomers may conveniently be effected by conventional techniques such as column chromatography.

The compounds according to the invention wherein the group F is an indazole moiety of structure FB as defined above may be prepared by a process which comprises the cyclisation of a compound of formula X:



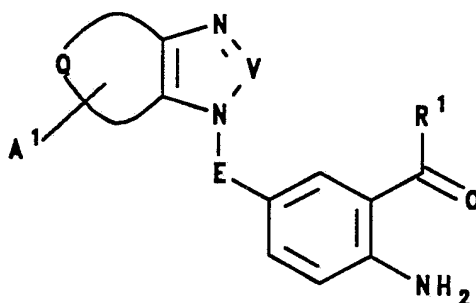
(X)

where Q, A¹, V, E and R¹ are as defined above; and D³ represents a readily displaceable group; followed, where required, by N-alkylation by standard methods to introduce the moiety R³.

The cyclisation of compound X is conveniently achieved in a suitable organic solvent at an elevated temperature, for example in a mixture of m-xylene and 2,6-lutidine at a temperature in the region of 140°C.

The readily displaceable group D³ in the compounds of formula X suitably represents a C₁₋₄ alkanoyloxy group, preferably acetoxy. Where D³ in the desired compound of formula X represents acetoxy, this compound may be conveniently prepared by treating a carbonyl compound of formula XI:

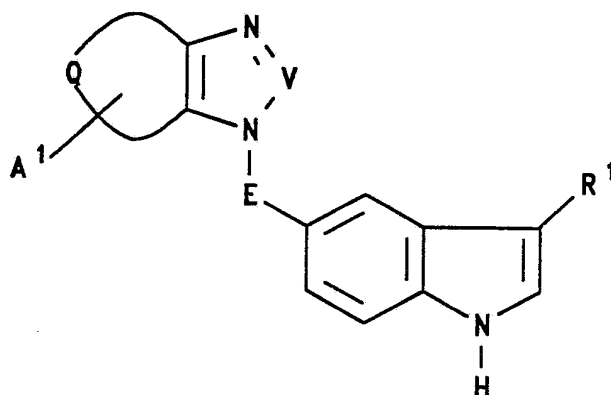
- 21 -



(XI)

wherein Q, A¹, V, E and R¹ are as defined above; or a
protected derivative thereof; with hydroxylamine
hydrochloride, advantageously in pyridine at the reflux
temperature of the solvent; followed by acetylation with
15 acetic anhydride, advantageously in the presence of a
catalytic quantity of 4-dimethylaminopyridine, in
dichloromethane at room temperature.

The N-formyl protected derivative of the
intermediate of formula XI may be conveniently prepared
20 by ozonolysis of an indole derivative of formula XII:



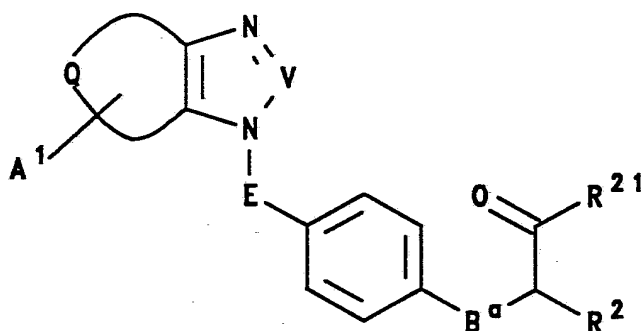
(XII)

wherein Q, A¹, V, E and R¹ are as defined above; followed
by a reductive work-up, advantageously using
dimethylsulphide.

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The indole derivative of formula XII may be prepared by methods analogous to those described in the accompanying Examples, or by procedures well known from the art.

5 In a further process, the compounds according to the invention wherein the group F is a benzofuran or benzthiophene moiety may be prepared by a method which comprises cyclising a compound of formula XIII:



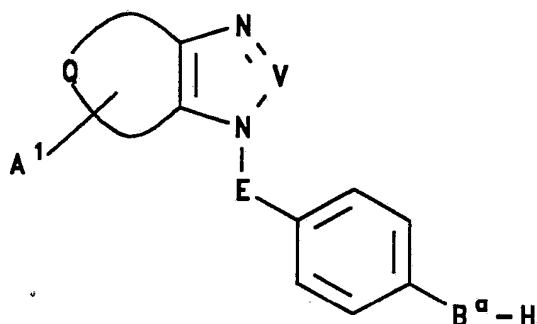
(XIII)

20 wherein Q, A¹, V, E and R² are as defined above, B^a represents oxygen or sulphur, and R²¹ corresponds to the group R¹ as defined above or represents a precursor group thereto as discussed below; followed, where required, by
 25 conversion of the group R²¹ into the desired group R¹ by conventional means.

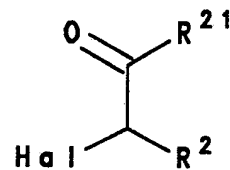
The cyclisation is conveniently effected by using polyphosphoric acid or a polyphosphate ester, advantageously at an elevated temperature.

30 The compounds of formula XIII may be prepared by reacting a compound of formula XIV with a compound of formula XV:

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(XIV)

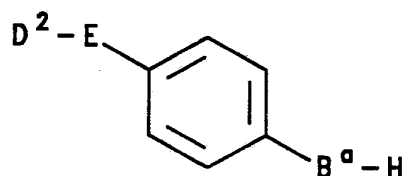


(XV)

wherein Q, A¹, V, E, B^a, R² and R²¹ are as defined above,
and Hal represents halogen.

15 The reaction is conveniently effected in the
presence of a base such as sodium hydroxide.

 The hydroxy and mercapto derivatives of formula
XIV may be prepared by a variety of methods which will be
readily apparent to those skilled in the art. In one
20 such method, a compound of formula VIII as defined above
is reacted with a compound of formula XVI:



(XVI)

wherein D², E and B^a are as defined above.

30 In a still further process, the compounds
according to the invention wherein E is other than a
chemical bond may be prepared by a process which
comprises reacting a compound of formula VIII as defined
above with a compound of formula D⁴-E¹-F, wherein F is as

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defined above, E¹ represents a straight or branched alkylene chain containing from 1 to 4 carbon atoms, and D⁴ represents a group which is capable of being displaced during the course of the reaction.

5 The displaceable group D⁴ suitably represents hydroxy, in which case the reaction is advantageously carried out in the presence of triphenylphosphine and diethyl azodicarboxylate, ideally in an organic solvent such as tetrahydrofuran at room temperature.

10 Alternatively, the group D⁴ may be a conventional leaving group such as a halogen atom, for example bromine, or a trialkylammonium group, for example trimethylammonium. Where D⁴ represents bromine, the reaction is conveniently carried out in the presence of a
15 mild base, e.g. potassium carbonate, suitably in an organic solvent such as N,N-dimethylformamide, at a temperature of between 10°C and 100°C, ideally at room temperature. Where D⁴ represents trimethylammonium, the reaction is conveniently carried out in the presence of a
20 strong base such as sodium hydride, suitably in an organic solvent such as N,N-dimethylformamide, and ideally at a temperature in the region of 90°C.

 As with that between compounds VIII and IX, the reaction between compounds VIII and D⁴-E¹-F, as well as
25 that between compounds VIII and XVI, is capable of giving rise to mixtures of positional isomers which, as before, may conveniently be separated by conventional techniques such as column chromatography.

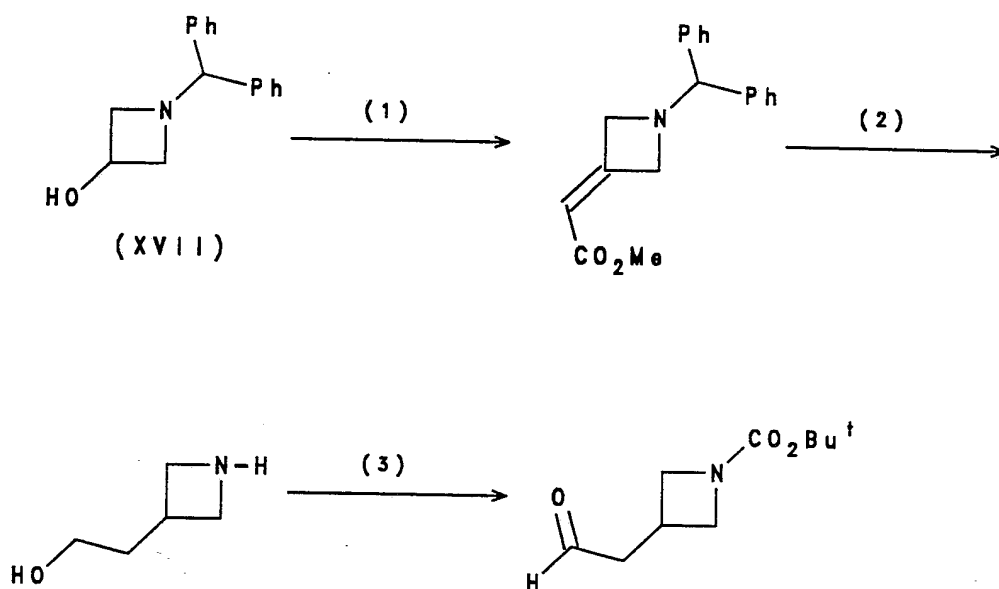
 Where they are not commercially available, the
30 intermediates of formula D⁴-E¹-F may be prepared by procedures analogous to those described in the accompanying Examples, or by methods well known from the art. For example, those compounds wherein D⁴ is halogen may be prepared from the corresponding compounds of

- 25 -

formula D⁴-E¹-F in which D⁴ is hydroxy using standard halogenation techniques. Alternatively, those compounds wherein D⁴ is a trialkylammonium group may be prepared from the corresponding compounds of formula D⁴-E¹-F in which D⁴ represents dialkylamino by quaternisation using a suitable alkyl iodide in conventional manner.

The intermediates of formula IV, VIII, IX, XV and XVI, where they are not commercially available, may be prepared by methods analogous to those described in the accompanying Examples, or by procedures known from the art. In particular, the intermediates of formula VIII may be prepared by procedures analogous to those described in Comprehensive Heterocyclic Chemistry, ed. A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, vol. 5.

The preparation of a typical protected azetidinyI intermediate of formula IVA is illustrated by the following reaction scheme:



The starting compound XVII is known from J. Chem. Soc., Chem Commun., 1968, 93. Step 1 of the

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reaction scheme comprises oxidation of the hydroxy group of compound XVII to a carbonyl group using pyridine.SO₃ in dimethyl sulphoxide (DMSO) and triethylamine; followed by reaction of the resulting azetidinone derivative with
5 the Horner-Emmons reagent MeO₂C.CH₂.PO(OEt)₂ in the presence of sodium hydride, using tetrahydrofuran (THF) as the solvent. In Step 2, the double bond of the azetidine olefin ester is hydrogenated over palladium-charcoal in methanol; the methyl ester group is then
10 reduced to hydroxymethyl by treatment with lithium aluminium hydride in THF; and the diphenylmethyl protecting group is in turn removed by treatment with palladium hydroxide on charcoal, with methanol serving as the solvent. Step 3 involves protection of the azetidine
15 nitrogen as the N-t-butoxycarbonyl (N-BOC) carbamate derivative; and, finally, Swern oxidation of the side chain terminal hydroxy group to an aldehyde moiety by treatment with oxalyl chloride in DMSO/triethylamine.

It will be understood that any compound of
20 formula I initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further compound of formula I by techniques known from the art. In particular, a compound of formula I wherein R³ is hydrogen initially obtained
25 may be converted into a compound of formula I wherein R³ represents C₁₋₆ alkyl by standard alkylation techniques, for example by treatment with an alkyl iodide, e.g. methyl iodide, typically under basic conditions, e.g. sodium hydride in dimethylformamide. Similarly, a
30 compound of formula I wherein R¹ represents a group of formula -CH₂.CHR⁴.NH₂ initially obtained may be converted into a compound of formula I wherein R¹ represents a group of formula -CH₂.CHR⁴.NR⁶R⁷ in which R⁶ and R⁷ independently represent C₁₋₆ alkyl, by conventional N-

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alkylation techniques, e.g. by treatment with the appropriate aldehyde in the presence of a reducing agent such as sodium cyanoborohydride.

5 Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography.

10 The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds may, for example, be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with
15 an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid followed by fractional crystallization and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric esters or amides,
20 followed by chromatographic separation and removal of the chiral auxiliary.

25 During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The
30 protecting groups may be removed at a convenient subsequent stage using methods known from the art.

Alternatively, certain of the functional groups on the desired products may be carried through the reaction sequence as precursor groups, and then

- 28 -

regenerated from these precursor groups at a late stage in the overall synthesis. For example, where R¹ in the desired compound of formula I represents a group of formula $-(CH_2)_2NH_2$, this group can be generated from a cyano precursor $-CH_2CN$ by reduction using, for example, borane/tetrahydrofuran. The cyano precursor may in turn be carried through the reaction sequence as a methyl group $-CH_3$, which may conveniently be converted to $-CH_2CN$ by treatment with N-bromosuccinimide and benzoyl peroxide, in the presence of a bright light source, followed by reaction of the resulting bromo intermediate with sodium cyanide in dimethyl sulphoxide.

The following Examples illustrate the preparation of compounds according to the invention.

The ability of test compounds to bind to 5-HT₁-like receptors was measured in membranes prepared from pig caudate using the procedure described in J. Neurosci., 1987, 7, 894. Binding was determined using 2 nM 5-hydroxytryptamine creatinine sulphate, 5-[1,2-³H(N)] as a radioligand. Cyanopindolol (100 nM) and mesulergine (100 nM) were included in the assay to block out 5-HT_{1A} and 5-HT_{1C} binding sites respectively. The concentration of the compounds of the accompanying Examples required to displace 50% of the specific binding (IC₅₀) is below 1 μM in each case.

The activity of test compounds as agonists of the 5-HT₁-like receptor was measured in terms of their ability to mediate contraction of the saphenous vein of New Zealand White rabbits, using the procedure described in Arch. Pharm., 1990, 342, 111. Agonist potencies were calculated as $-\log_{10}EC_{50}$ (pEC₅₀) values, from plots of percentage 5-HT (1 μM) response against the concentration of the agonist. The compounds of the accompanying

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Examples were found to possess pEC_{50} values in this assay of not less than 5.0 in each case.

- 30 -

EXAMPLE 1

N,N-Dimethyl-2-[5-(4-azabenzimidazol-1-yl)-1H-indol-3-yl]
ethylamine. Oxalate. Monohydrate.

1. 4-(4-Azabenzimidazol-1-yl)nitrobenzene

5

Sodium hydride (2.02g, 84.0mmol, 60% dispersion in oil) was added to a solution of 4-azabenzimidazole (10.0g, 84.0mmol) in DMF (120ml). The mixture was stirred at room temperature for 0.25h before adding 1-fluoro-4-nitrobenzene (11.86g, 84.0mmol) and stirring for 2h. A precipitate formed which was filtered off and washed with Et₂O (100ml) and acetone (50ml). The product was dried under vacuum to afford the title-product (10.0g, 50%); δ (250MHz, D₆-DMSO) 7.40-7.48 (1H, m, Ar-H), 8.06 (2H, d, J = 9.0Hz, Ar-H), 8.24 (1H, d, J = 9.0Hz, Ar-H), 8.46 (2H, d, J = 9.0Hz, Ar-H), 8.56 (1H, dd, J = 1.0 and 3.5Hz, Ar-H), 9.04 (1H, s, Ar-H).

10

15

2. 4-(4-Azabenzimidazol-1-yl)phenylaniline

10% Pd-C (1.0g) was added to a mixture of the preceding nitrobenzene (10.0g, 42.0mmol), 1N HCl (350ml) and methanol (200ml) and hydrogenated at 40 psi in a Parr flask for 3h. The catalyst was removed by filtration through celite and the solvent removed under vacuum. The residue was taken up into H₂O (20ml), basified (K₂CO₃) and extracted with CH₂Cl₂ (5 x). The combined extracts were dried (Na₂SO₄) and evaporated and the residue chromatographed on silica gel, eluting with CH₃Cl₂/MeOH (95:5) to give the desired aniline (6.45g, 74%); δ (360MHz, CD₂OD) 6.76 (2H, d, J = 9.0Hz, Ar-H), 7.18 (2H, d, J = 9.0Hz, Ar-H), 7.27 (1H, dd, J = 5.0 and 8.0Hz, Ar-H), 7.84 (1H, dd, J = 1.0 and 8.0Hz, Ar-H), 8.37 (1H, dd, J = 1.5 and 5.0Hz, Ar-H), 8.41 (1H, s, Ar-H).

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3. 4-(4-Azabenzimidazol-1-yl)phenylhydrazine

A solution of NaNO_2 (2.35g, 34.0mmol) in H_2O (30ml) was added to a stirred solution of the preceding aniline (6.45g, 31.0mmol) in concⁿ. HCl (60ml), cooled to -15°C . After addition the mixture was stirred for 0.5h at -15°C and then filtered through a sinter directly into an addition funnel. The resulting solution was added to a rapidly stirred solution of $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (28.0g, 0.12mol) in concⁿ. HCl (50ml) at such a rate as to maintain the temperature below -5°C . The mixture was warmed to room temperature, the precipitate filtered off and washed several times with Et_2O . In order to remove tin salts from the product the free base was generated by dissolving in H_2O (20ml), basifying with NH_4OH and extracting with CH_2Cl_2 (7 x). The combined extracts were dried (MgSO_4) and the solvent removed under vacuum to give the desired hydrazine (5.1g, 74%); δ (250MHz, CD_3OD) 7.20 (2H, d, $J = 9.0\text{Hz}$, Ar-H), 7.28-7.54 (3H, m, Ar-H), 8.08 (1H, dd, $J = 1.5$ and 8.0Hz , Ar-H), 8.62 (1H, dd, $J = 1.5$ and 5.0Hz , Ar-H), 8.67 (1H, s, Ar-H).

4. N,N-Dimethyl-2-[5-(4-azabenzimidazol-1-yl)-1H-indol-3-yl]ethylamine. Oxalate. Monohydrate.

N,N-Dimethylbutanal dimethylacetal (0.36g, 2.2mmol) was added to a solution of the preceding hydrazine (0.5g, 2.2mmol) in 4% H_2SO_4 (20ml) and the mixture refluxed for 16h. The solution was cooled to room temperature, basified with ammonia solution and extracted with CH_2Cl_2 (3 x 100ml). The combined extracts were dried (Na_2SO_4) and evaporated and the residue chromatographed on silica-gel eluting with $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_3$ (60:8:1) to give the desired indole (0.25g). The oxalate monohydrate salt was prepared by adding a solution of oxalic acid in ether to a solution of the free base in $\text{MeOH}/\text{Et}_2\text{O}$; mp $116-118^\circ\text{C}$; (Found: C, 58.40; H, 5.81; N, 16.89. $\text{C}_{18}\text{H}_{19}\text{N}_5\text{C}_2\text{H}_2\text{O}_4 \cdot \text{H}_2\text{O}$ requires C, 58.10; H, 5.61; N, 16.94%); δ

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(360MHz, D₂O) 2.93 (6H, s, NMe₂), 3.14 (2H, t, J = 7.5Hz, CH₂), 3.44 (2H, t, J = 7.5Hz, CH₂), 7.17 (1H, dd, J = 1.8 and 8.6Hz, Ar-H), 7.28 (1H, dd, J = 4.9 and 7.2Hz, Ar-H), 7.39 (1H, s, Ar-H), 7.51 (1H, d, J = 8.6Hz, Ar-H), 7.57 (1H, d, J = 1.8Hz, Ar-H), 7.83 (1H, d, J = 7.2Hz, Ar-H), 8.41 (1H, d, J = 4.9Hz, Ar-H), 8.48 (1H, s, Ar-H).

EXAMPLE 2

N,N-Dimethyl-2-[5-(4,6-diazabenzimidazol-1-yl)-1H-indol-3-yl]ethylamine. Sesquioxalate.

10 1. 4-(4,6-Diazabenzimidazol-1-yl)nitrobenzene

Prepared from purine and 1-fluoro-4-nitrobenzene as described for Example 1, Step 1. The product precipitated from the reaction mixture as a single isomer; δ (D₆-DMSO) 8.16 (2H, d, J = 9.0Hz, Ar-H), 8.48 (2H, d, J = 9.0Hz, Ar-H), 9.13 (1H, s, Ar-H), 9.28 (1H, s, Ar-H), 9.39 (1H, s, Ar-H).

20 2. 4-(4,6-Diazabenzimidazol-1-yl)phenylhydrazine. Dihydrochloride.

Prepared from the preceding nitrobenzene as described for Example 1, Steps 2 and 3; δ (360MHz, D₂O) 7.30 (2H, d, J = 8.8Hz, Ar-H), 7.74 (2H, d, J = 8.8Hz, Ar-H), 9.39 (1H, s, Ar-H), 9.43 (1H, s, Ar-H), 9.58 (1H, s, Ar-H).

25 3. 2-[5-(4,6-Diazabenzimidazol-1-yl)-1H-indol-3-yl] ethylamine

4-Chlorobutanal dimethylacetal (0.66g, 4.3mmol) was added to a solution of the preceding hydrazine (1.1g, 3.9mmol) in EtOH/H₂O (50ml, 5:1) and the mixture refluxed for 3h. The resultant precipitate

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was filtered off, taken up into 2N NaOH (10ml) and extracted with CH_2Cl_2 (4 x 50ml). The combined extracts were dried (Na_2SO_4) and evaporated to give the title-tryptamine (0.15g); δ (360MHz, CD_3OD) 3.06-3.20 (6H, m, 2 of CH_2), 7.32 (1H, s, Ar-H), 7.34 (1H, dd, J = 1.7 and 8.5Hz, Ar-H), 7.57 (1H, d, J = 8.5Hz, Ar-H), 7.82 (1H, d, J = 1.7Hz, Ar-H), 8.81 (1H, s, Ar-H), 8.99 (1H, s, Ar-H), 9.02 (1H, s, Ar-H).

4. N,N-Dimethyl-2-[5-(4,6-diazabenzimidazol-1-yl)-1H-indol-3-yl] ethylamine. Sesquioxalate.

A solution of formaldehyde (0.18g of a 38% ww solution in H_2O , 2.2mmol) in MeOH (25ml) was added to a stirred solution of the preceding tryptamine (0.23g, 0.83mmol), NaCNBH_3 (0.134g, 2.08mmol) and MeCO_2H (0.275g, 4.7mmol), in MeOH (25ml), at room temperature. After 2h, a saturated solution of K_2CO_3 (10ml) was added and the solvent removed under vacuum. The aqueous residue was extracted with ethyl acetate (3 x 50ml), the combined extracts dried (Na_2SO_4) and evaporated. The crude product was chromatographed on silica-gel eluting with $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_3$ (50:8:1) to give the title-product. The sesquioxalate salt was prepared, mp 208-210°C (MeOH); (Found: C, 54.24; H, 5.08; N, 19.07. $\text{C}_{17}\text{H}_{18}\text{N}_6 \cdot 1.5(\text{C}_2\text{H}_2\text{O}_4)$ requires C, 54.42; H, 4.80; N, 19.04%); δ (360MHz, D_2O) 2.94 (6H, s, NMe_2), 3.14 (2H, t, J = 7.0Hz, CH_2), 3.48 (2H, t, J = 7.0Hz, CH_2), 7.25 (1H, d, J = 8.3Hz, Ar-H), 7.38 (1H, s, Ar-H), 7.45 (1H, d, J = 8.3Hz, Ar-H), 7.64 (1H, s, Ar-H), 8.80 (1H, s, Ar-H), 8.93 (2H, s, Ar-H).

EXAMPLE 3

N,N-Dimethyl-2-[5-(4,6-diazabenzimidazol-1-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate.

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1. 4-Cyanophenylhydrazine. Hydrochloride

To a cooled (-15°C) and stirred suspension of 4-aminobenzonitrile (50g, 423mmol) in concentrated hydrochloric acid (550ml) was added dropwise a solution of sodium nitrite (31.5g, 457mmol) in water (200ml) at such a rate as to maintain the temperature below -10°C. After the addition was finished, the reaction mixture was quickly filtered to remove solids and the filtrate was added portionwise to a cooled (-20°C) and stirred solution of tin (II) chloride dihydrate (477g, 2.1mol) in concentrated hydrochloric acid (370ml) at such a rate as to maintain the temperature below -10°C. After further 15 minutes at -10 to 0°C, the white precipitate was collected by filtration, washed with diethyl ether (4 x 250ml) and dried to give 56g (78%) of the title compound; mp 235-237°C (ethanol-water 1:1); ¹H NMR (250MHz, D₆-DMSO) δ 10.50 (3H, br s, -N⁺H₃), 9.10 (1H, br s, -NH-), 7.71 (2H, d, J = 8.8Hz, Ar-H), 7.03 (2H, d, J = 8.8Hz, Ar-H); m/z (CI) 132 (M⁺-1).

2. 2-[5-Cyano-1H-indol-3-yl]ethylamine. Hydrochloride.

To a stirred suspension of 4-cyanophenylhydrazine (50g) in a mixture of ethanol and water (5:1; 21) was added 4-chlorobutanal dimethylacetal (45g) and the resulting mixture was refluxed for 18 hours. Solvents were removed under vacuum and the residue was azeotroped with toluene to give a brown solid. Crystallisation of this crude material from methanol (150ml) gave 23g (35%) of the title compound as a yellow solid; mp 270-274°C; ¹H NMR (250MHz, D₆-DMSO) δ 11.60 (1H, br s, indole N-H), 8.17 (1H, d, J = 1.1Hz, Ar-H), 7.97 (3H, br s, -N⁺H₃), 7.54 (1H, d, J = 8.5Hz, Ar-H), 7.46 (1H, s, Ar-H), 7.44 (1H, dd, J = 8.5 and 1.1Hz, Ar-H), 3.05 (4H, br s, -CH₂CH₂N-); m/z (CI) 184 (M⁺-1).

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3. N-tert-Butyloxycarbonyl-2-[5-cyano-1H-indol-3-yl]ethylamine.

The title compound was prepared in 58% yield from the preceding tryptamine using $(\text{BOC})_2\text{O}$ and NEt_3 in CH_2Cl_2 . The product was obtained as a white solid; mp 132-134°C (hexane-ethyl acetate); ^1H NMR (250MHz, CDCl_3) δ 8.42 (1H, br s, indole N-H), 7.93 (1H, s, Ar-H), 7.41 (2H, s, Ar-H), 7.12 (1H, d, $J = 2.2\text{Hz}$, Ar-H), 4.71 (1H, br s, -NH-), 3.44 (2H, q, $J = 6.9\text{Hz}$, $-\text{CH}_2\text{NH}-$), 2.94 (2H, t, $J = 6.9\text{Hz}$, Ar- CH_2-), 1.45 (9H, s, t-Bu); m/z (CI) 286 ($\text{M}^+ + 1$).

4. N-tert-Butyloxycarbonyl-2-[5-aminomethyl-1H-indol-3-yl]ethylamine

A solution of the product from the previous step (11.3g) in a mixture of absolute ethanol (750ml) and chloroform (22ml) was hydrogenated at 50 psi over platinum (IV) oxide (1g) for 28 hours. The catalyst was removed by filtration and solvents were removed under vacuum. Flash chromatography of the residue (silica gel, dichloromethane-methanol-ammonia 90:10:1) gave 9.5g (82%) of the title compound as a white solid; mp 147-149°C; ^1H NMR (360MHz, CDCl_3) δ 8.04 (1H, br s, indole N-H), 7.52 (1H, s, Ar-H), 7.33 (1H, d, $J = 8.4\text{Hz}$, Ar-H), 7.16 (1H, d, $J = 8.4\text{Hz}$, Ar-H), 7.03 (1H, s, Ar-H), 4.61 (1H, br s, -NHBOC), 3.96 (2H, s, Ar- CH_2NH_2), 3.45 (2H, br q, $-\text{CH}_2\text{NHBOC}$), 2.95 (2H, t, $J = 6.8\text{Hz}$, Ar- CH_2-), 1.43 (9H, s, t-Bu); m/z (CI) 288 ($\text{M}^+ - 1$).

5. N-tert-Butyloxycarbonyl-2-[5-dimethylaminomethyl-1H-indol-3-yl]ethylamine

The title compound was prepared in 71% yield from the product from the previous step using the conditions described for Example 2,

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Step 4; colourless thick oil; ^1H NMR (250MHz, CDCl_3) δ 8.07 (1H, br s, indole N-H), 7.50 (1H, s, Ar-H), 7.31 (1H, d, $J = 8.3\text{Hz}$, Ar-H), 7.16 (1H, d, $J = 8.3\text{Hz}$, Ar-H), 7.02 (1H, s, Ar-H), 4.61 (1H, br s, -NH-), 3.54 (2H, s, Ar- CH_2N -), 3.45 (2H, q, $J = 6.2\text{Hz}$, - CH_2NH -), 2.94 (2H, t, $J = 6.2\text{Hz}$, Ar- CH_2 -), 2.27 (6H, s, - NMe_2), 1.43 (9H, s, t-Bu).

6. N-tert-Butyloxycarbonyl-2-[5-trimethylammonium methyl-1H-indol-3-yl]ethylamine. Iodide.

A solution of the product from step 5 (2.9g) in a mixture of anhydrous diethyl ether (170ml) and iodomethane (36ml) was allowed to stand at room temperature for 16 hours in the dark. The white solid was collected by filtration, washed with diethyl ether and dried over phosphorous pentoxide at 50°C under vacuum to give 4.2g (100%) of the title compound; mp $199\text{--}202^\circ\text{C}$ (decomposition); ^1H NMR (360MHz, DMSO-d_6) δ 11.09 (1H, br s, indole N-H), 7.69 (1H, s, Ar-H), 7.44 (1H, d, $J = 8.3\text{Hz}$, Ar-H), 7.26 (1H, s, Ar-H), 7.19 (1H, d, $J = 8.3\text{Hz}$, Ar-H), 6.89 (1H, br t, -NH-), 4.57 (2H, s, Ar- CH_2N -), 3.23 (2H, q, $J = 7.6\text{Hz}$, - CH_2NH -), 3.01 (9H, s - N^+Me_3), 2.83 (2H, t, $J = 7.6\text{Hz}$, Ar- CH_2 -), 1.37 (9H, s, t-Bu); m/z (FAB) 332. (Found: C, 49.30; H, 6.55; N, 8.79. $\text{C}_{19}\text{H}_{30}\text{IN}_3\text{O}_2$ requires: C, 49.68; H, 6.58; N, 9.15%).

7. N-(tert-Butyloxycarbonyl-2-[5-(4,6-diazabenzimidazol-1-yl)methyl]-1H-indol-3-yl]ethylamine

Sodium hydride (0.185g, 7.7mmol, 60% dispersion in oil) was added to a stirred solution purine (0.5g, 4.2mmol) in DMF (50ml). The mixture was stirred at room temperature for 0.25h before adding the preceding methiodide (1.0g, 2.2mmol) and refluxing for 16h. The solution was cooled to room temperature before adding H_2O (50ml) and extracting with EtOAc (3 x). The combined organics were washed with brine (2 x), dried (Na_2SO_4) and evaporated. The crude product was

- 37 -

purified by chromatography on silica-gel eluting with EtOAc/MeOH/NH₃ (90:2:0.5 _ 50:6:0.5) to give 2 products. The less polar isomer (0.14g) was identified as the 5,7-diazabenzimidazole adduct; δ (360MHz, CDCl₃) 1.46 (9H, s, (CH₃)₃), 2.96 (2H, t, J = 7.0Hz, CH₂), 3.38-3.52 (2H, m, CH₂), 5.54 (2H, s, CH₂), 7.08 (1H, d, J = 1.5Hz, Ar-H), 7.16 (1H, dd, J = 1.5 and 8.5Hz, Ar-H), 7.34 (1H, d, J = 8.5Hz, Ar-H), 7.64 (1H, s, Ar-H), 8.06 (1H, s, Ar-H), 8.46 (1H, br s, NH), 9.04 (1H, s, Ar-H), 9.14 (1H, s, Ar-H). The more polar product was identified as the title-tryptamine (0.55g) δ (360MHz, CDCl₃) 1.43 (9H, s, (CH₃)₃), 2.93 (2H, t, J = 6.8Hz, CH₂), 3.43 (2H, br s, CH₂), 5.52 (2H, s, CH₂), 7.04 (1H, d, J = 8.3Hz, Ar-H), 7.12 (1H, s, Ar-H), 7.27 (1H, s, Ar-H), 7.37 (1H, d, J = 8.3Hz, Ar-H), 7.61 (1H, s, N-H), 8.30 (1H, s, Ar-H), 8.49 (1H, s, N-H), 8.76 (1H, s, Ar-H), 9.10 (1H, s, Ar-H).

15 8. 2-[5-(4,6-Diazabenzimidazol-1-ylmethyl)-1H-indol-3-yl]ethylamine

The preceding NHBOC-tryptamine (0.45g, 1.1mmol) was added to 90% formic acid (50ml), at 0°C. The mixture was warmed to room temperature and stirred for 4h before adding methanol (50ml) and evaporating the solvents under vacuum. The residue was chromatographed on silica-gel eluting with CH₂Cl₂/MeOH/NH₃ (30:8:1) to afford the title-tryptamine (69mg); δ (360MHz, CD₃OD) 2.86-2.91 (4H, m, 2 of CH₂), 5.58 (2H, s, CH₂), 7.06 (1H, dd, J = 1.5 and 8.4Hz, Ar-H), 7.07 (1H, s, Ar-H), 7.29 (1H, d, J = 8.4Hz, Ar-H), 7.61 (1H, s, Ar-H), 8.64 (1H, s, Ar-H), 8.79 (1H, s, Ar-H), 8.84 (1H, s, Ar-H).

30 9. N,N-Dimethyl-2-[5-(4,6-diazabenzimidazol-1-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate.

Prepared from the preceding tryptamine using the procedure described for Example 2, Step 4. The oxalate salt was prepared, mp

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210-212°C (¹PrOH/MeOH/Et₂O); (Found: C, 57.36; H, 5.44; N, 19.21. C₁₈H₂₀N₆·1.2 (C₂H₂O₄) requires C, 57.19; H, 5.27; N, 19.61%); δ (360MHz, D₂O) 2.89 (6H, s, NMe₂), 3.20 (2H, t, J = 7.4Hz, CH₂), 3.44 (2H, t, J = 7.4Hz, CH₂), 5.65 (2H, s, CH₂), 7.22 (1H, d, J = 8.4Hz, Ar-H), 7.35 (1H, s, Ar-H), 7.50 (1H, s, Ar-H), 7.68 (1H, s, Ar-H), 8.74 (1H, s, Ar-H), 8.88 (1H, s, Ar-H), 8.91 (1H, s, Ar-H).

EXAMPLE 4

10 N,N-Dimethyl-2-[5-(5,7-diazabenzimidazol-1-ylmethyl)-1H-indol-3-yl]ethylamine. Sesquioxalate. Hemihydrate.

1. 2-[5-(5,7-Diazabenzimidazol-1-ylmethyl)-1H-indol-3-yl]ethylamine

15 Prepared from N-tert-butyloxycarbonyl-2-[5-(5,7-diazabenzimidazol-1-ylmethyl)-1H-indol-3-yl]ethylamine using the procedure described for Example 3, Step 8; δ (250MHz, CDCl₃) 2.88 (2H, t, J = 7.4Hz, CH₂), 3.02 (2H, t, J = 7.4Hz, CH₂), 5.56 (2H, s, CH₂), 7.08 (1H, d, J = 1.5Hz, Ar-H), 7.18 (1H, dd, J = 1.5 and 8.4Hz, Ar-H), 7.34 (1H, d, J = 8.4Hz, Ar-H), 7.64 (1H, s, Ar-H), 8.06 (1H, s, Ar-H), 20 8.44 (1H, br s, NH), 9.04 (1H, s, Ar-H), 9.16 (1H, s, Ar-H).

2. N,N-Dimethyl-2-[5,7-diazabenzimidazol-1-ylmethyl)-1H-indol-3-yl]ethylamine. Sesquioxalate. Hemihydrate.

25 Prepared from the preceding tryptamine using the procedure described for Example 2, Step 4. The sesquioxalate hemihydrate salt was prepared, mp 105-107°C (¹PrOH/MeOH/NH₃); (Found: C, 54.02; H, 5.62; N, 17.99. C₁₈H₂₀N₆·1.5(C₂H₂O₄)·0.7H₂O requires C, 53.89; H, 5.25; N, 17.96%); δ (360MHz, D₂O) 2.89 (6H, s, NMe₂), 3.19 (2H, t, J = 7.4Hz, CH₂), 3.45 (2H, t, J = 7.4Hz, CH₂), 5.60 (2H, s, CH₂), 7.22 (1H, 30 7.4Hz, CH₂), 3.45 (2H, t, J = 7.4Hz, CH₂), 5.60 (2H, s, CH₂), 7.22 (1H,

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dd, J = 1.5 and 8.4Hz, Ar-H), 7.33 (1H, s, Ar-H), 7.48 (1H, d, J = 8.4Hz, Ar-H), 7.66 (1H, s, Ar-H), 8.58 (1H, s, Ar-H), 8.94 (1H, s, Ar-H), 9.12 (1H, s, Ar-H).

5

EXAMPLE 5Tablet Preparation

Tablets containing 1.0, 2.0, 25.0, 26.0, 50.0 and 100.0mg, respectively of the following compounds are prepared as illustrated below:

10

N,N-Dimethyl-2-[5-(4-azabenzimidazol-1-yl)-1H-indol-3-yl]ethylamine. Oxalate. Monohydrate.

15

N,N-Dimethyl-2-[5-(4,6-diazabenzimidazol-1-yl)-1H-indol-3-yl]ethylamine. Sesquioxalate.

N,N-Dimethyl-2-[5-(4,6-diazabenzimidazol-1-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate.

N,N-Dimethyl-2-[5-(5,7-diazabenzimidazol-1-ylmethyl)-1H-indol-3-yl]ethylamine. Sesquioxalate. Hemihydrate.

20

TABLE FOR DOSES CONTAINING FROM
1-25MG OF THE ACTIVE COMPOUND

	Active Compound	Amount-mg		
		1.0	2.0	25.0
25	Microcrystalline cellulose	49.25	48.75	37.25
	Modified food corn starch	49.25	48.75	37.25
	Magnesium stearate	0.50	0.50	0.50

- 40 -

TABLE FOR DOSES CONTAINING FROM
26-100MG OF THE ACTIVE COMPOUND

	Active Compound	26.0	50.0	100.0
5	Microcrystalline cellulose	52.0	100.0	200.0
	Modified food corn starch	2.21	4.25	8.5
	Magnesium stearate	0.39	0.75	1.5

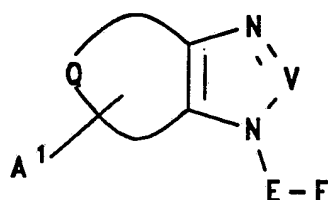
10 All of the active compound, cellulose, and a portion of the corn starch are mixed and granulated to 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 1.0mg, 2.0mg, 25.0mg, 26.0mg, 50.0mg and 100mg of the active ingredient per tablet.

15

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CLAIMS:

1. A compound of formula I, or a salt or
5 prodrug thereof:



(I)

wherein

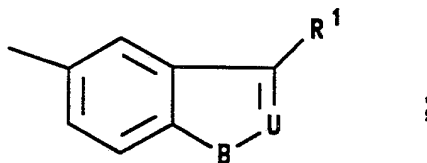
- 15 Q represents the residue of a six-membered aromatic or heteroaromatic nucleus containing zero, one or two nitrogen atoms;

- A¹ represents hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, -OR^x, -SR^x, -NR^xR^y, -NR^xCOR^y, -NR^xCO₂R^y, -NR^xSO₂R^y, or
20 -NR^xCTNR^xR^y;

V represents nitrogen or C-A²;

- E represents a bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms;

- 25 F represents a group of formula

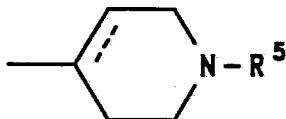


U represents nitrogen or C-R²;

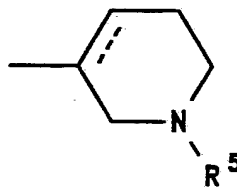
- 42 -

B represents oxygen, sulphur or $N-R^3$;

R^1 represents $-CH_2.CHR^4.NR^6R^7$ or a group of formula (i), (ii), (iii) or (iv):



(i)



(ii)



(iii)



(iv)

20 in which the broken line represents an optional chemical bond;

A^2 , R^2 , R^3 , R^4 , R^5 , R^6 and R^7 independently represent hydrogen or C_{1-6} alkyl;

25 R^x and R^y independently represent hydrogen, hydrocarbon or a heterocyclic group, or R^x and R^y together represent a C_{2-6} alkylene group;

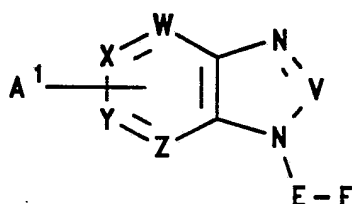
R^z represents hydrogen, hydrocarbon or a heterocyclic group;

30 T represents oxygen, sulphur or a group of formula $=N.G$; and

G represents hydrocarbon, a heterocyclic group or an electron-withdrawing group.

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2. A compound as claimed in claim 1 represented by structure IA:



(IA)

in which zero, one or two of W, X, Y and Z represent nitrogen and the remainder represent carbon; and A¹, V, E and F are as defined in claim 1.

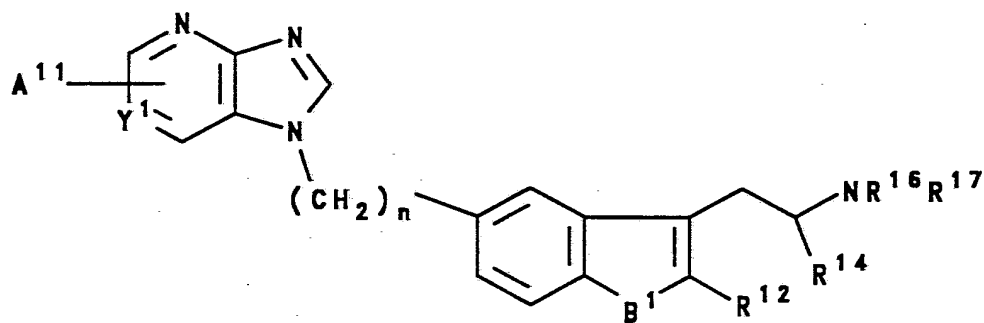
15 3. A compound as claimed in claim 2 wherein W represents nitrogen, X and Z each represents carbon and Y represents nitrogen or carbon.

20 4. A compound as claimed in claim 2 wherein Z represents nitrogen, W and Y each represents carbon and X represents nitrogen or carbon.

25 5. A compound as claimed in claim 1 represented by formula IIA, and salts and prodrugs thereof:

30

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(IIA)

wherein

Y¹ represents nitrogen or carbon;

n is zero, 1, 2 or 3;

15 B¹ represents oxygen, sulphur or N-R¹³;

A¹¹ represents C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, heteroaryl, heteroaryl(C₁₋₆)alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkylamino or
 20 di(C₁₋₆)alkylamino, any of which groups may be optionally substituted; or hydrogen, halogen, cyano, trifluoromethyl or amino; and

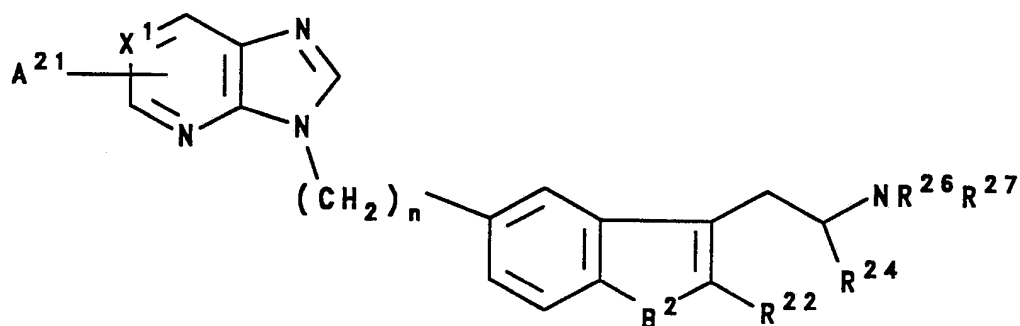
R¹², R¹³, R¹⁴, R¹⁶ and R¹⁷ independently represent hydrogen or C₁₋₆ alkyl.

25

6. A compound as claimed in claim 1 represented by formula IIB, and salts and prodrugs thereof:

30

- 45 -



(I I B)

wherein

X¹ represents nitrogen or carbon;

n is zero, 1, 2 or 3;

15 B² represents oxygen, sulphur or N-R²³;

A²¹ represents C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, heteroaryl, heteroaryl(C₁₋₆)alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkylamino or
 20 di(C₁₋₆)alkylamino, any of which groups may be optionally substituted; or hydrogen, halogen, cyano, trifluoromethyl or amino; and

R²², R²³, R²⁴, R²⁶ and R²⁷ independently represent
 25 hydrogen or C₁₋₆ alkyl.

7. A compound as claimed in claim 1 selected from:

N,N-dimethyl-2-[5-(4-azabenzimidazol-1-yl)-1H-indol-3-yl]ethylamine;

30 N,N-dimethyl-2-[5-(4,6-diazabenzimidazol-1-yl)-1H-indol-3-yl]ethylamine;

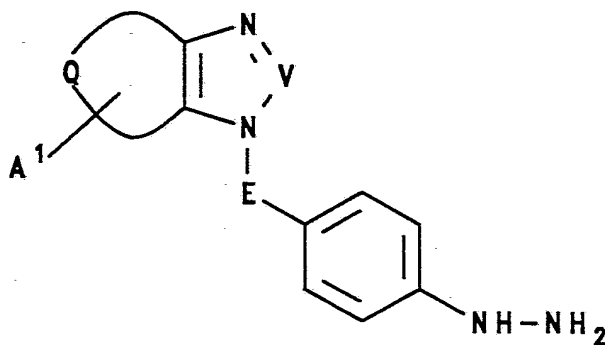
N,N-dimethyl-2-[5-(4,6-diazabenzimidazol-1-ylmethyl)-1H-indol-3-yl]ethylamine;

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N,N-dimethyl-2-[5-(5,7-diazabenzimidazol-1-ylmethyl)-1H-indol-3-yl]ethylamine;
and salts and prodrugs thereof.

- 5 8. A pharmaceutical composition comprising a compound as claimed in any one of the preceding claims in association with a pharmaceutically acceptable carrier or excipient.
- 10 9. A compound as claimed in any one of claims 1 to 7 for use in therapy.
- 15 10. The use of a compound as claimed in any one of claims 1 to 7 for the manufacture of a medicament for the treatment and/or prevention of clinical conditions for which a selective agonist of 5-HT₁-like receptors is indicated.
- 20 11. A process for the preparation of a compound as claimed in any one of claims 1 to 7 which comprises:

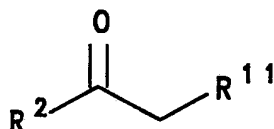
(A) reacting a compound of formula III:



(III)

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wherein Q, A¹, V and E are as defined in claim 1; with a compound of formula IV or a carbonyl-protected form thereof:

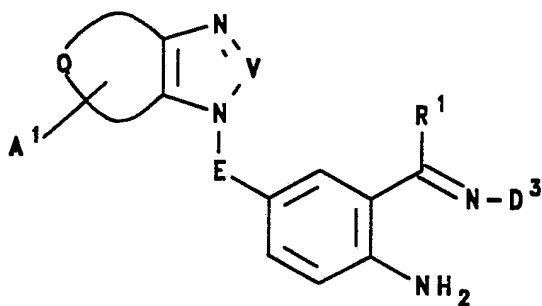


(IV)

- 10 wherein R² is as defined in claim 1 and R¹¹ corresponds to the group R¹ as defined in claim 1 or a protected derivative thereof, or represents a group of formula -CH₂.CHR⁴D¹, in which R⁴ is as defined in claim 1 and D¹ represents a readily displaceable group; followed, where
 15 required, by N-alkylation by standard methods to introduce the moiety R³; and, if necessary, by removal of any protecting groups; or

(B) cyclisation of a compound of formula X:

20

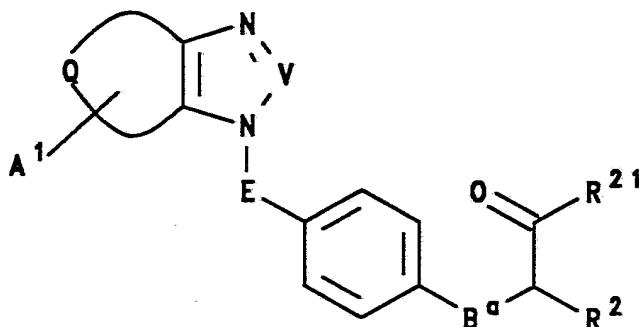


(X)

- 30 where Q, A¹, V, E and R¹ are as defined in claim 1, and D³ represents a readily displaceable group; followed, where required, by N-alkylation by standard methods to introduce the moiety R³; or

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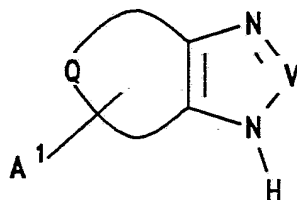
(C) cyclising a compound of formula XIII:



(XIII)

wherein Q, A¹, V, E and R² are as defined in claim 1, B¹ represents oxygen or sulphur, and R²¹ corresponds to the group R¹ as defined in claim 1 or represents a precursor group thereto; followed, where required, by conversion of the group R²¹ into the desired group R¹ by conventional means; or

(D) reacting a compound of formula VIII:



(VIII)

wherein Q, A¹ and V are as defined in claim 1; with a compound of formula D⁴-E¹-F, wherein F is as defined in claim 1, E¹ represents a straight or branched alkylene chain containing from 1 to 4 carbon atoms, and D⁴ represents a group which is capable of being displaced during the course of the reaction; and

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E) subsequently, where required, converting a compound of formula I initially obtained into a further compound of formula I by conventional methods.

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12. A method for the treatment and/or prevention of clinical conditions for which a selective agonist of 5-HT₁-like receptors is indicated, which method comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined in claim 1, or a pharmaceutically acceptable salt thereof or a prodrug thereof.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 93/00936

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 C07D471/04; C07D487/04;	C07D473/00; /(C07D471/04,235:00,221:00)	A61K31/435; A61K31/52
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	C07D ; A61K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	EP,A,0 313 397 (WELLCOME) 26 April 1989 see claims 1,5 ---	1,8
A	WO,A,9 206 973 (PFIZER) 30 April 1992 see claims 1,5 ---	1,8
A	EP,A,0 200 322 (LUNDBECK) 5 November 1986 see page 3, line 12 - line 15; claim 1 -----	1,8
<p>¹⁰ Special categories of cited documents :¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
25 AUGUST 1993	- 9. 09. 93	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	ALFARO FAUS I.	

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB93/00936

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 12 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

GB 9300936
SA 74356

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 25/08/93

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0313397	26-04-89	AU-A-	2418188	27-04-89
		DE-A-	3881472	08-07-93
		JP-A-	1146882	08-06-89
		US-A-	5225431	06-07-93

WO-A-9206973	30-04-92	AU-A-	8950491	20-05-92
		CA-A-	2091562	16-04-92
		CN-A-	1062529	08-07-92

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		CA-A-	1256437	27-06-89
		JP-A-	61236764	22-10-86
		US-E-	RE34299	29-06-93
		US-A-	4710500	01-12-87
